APPENDIX 7

Clinical Implications of the Differences in Dissolution and Absorption Characteristics of Oral Estrogen Therapy Agents

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Introduction

Physicians have long recognized the unique therapeutic role of estrogen replacement therapy (ERT) in providing relief from many of the symptoms associated with menopause. As menopause typically occurs at around the age of 50, and the life expectancy of the average woman today exceeds 80 years, it is likely that much of the female population will experience post-menopausal symptoms.[1]

Perhaps the most widely recognized of all such symptoms are hot flashes and night sweats, the intense sensation of flushing and increase in temperature that affects the upper body, particularly the face, hands and chest. Other common menopausal complaints include vaginal irritation, diminished libido, dyspareunia, sleep disturbance and deprivation, cognitive and memory disruptions, emotional disorders and a decline in the woman's overall quality of life. Administration of estrogen to overcome the hormonal imbalance that accompanies menopause is known to be effective in decreasing these symptoms, and also to reduce the long-term development of osteoporosis.[2,3]

In recent years, investigative efforts have been directed toward evaluating potential pharmacological distinctions between available estrogen formulations. Among the important issues that are being

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investigated are differences in dissolution and absorption characteristics between various estrogen products, and their impact on product efficacy, safety and tolerability.[4-6] In addition, substantive questions can be raised concerning the potential effect of gastric pH on the pharmacokinetics of the various oral estrogenic agents currently available. It is possible that concomitant administration of an antacid preparation such as Tums®, or a proton pump inhibitor such as omeprazole or lansoprazole, to treat the common co-existing medical condition gastroesophageal reflux disease (GERD), may neutralize gastric acidity and thus adversely affect the anticipated modified-release characteristics of some estrogen-containing products.

This communication will describe the development of estrogen replacement therapy from a historical perspective, and will review more recent scientific data that underscore the importance of selecting an appropriate estrogen formulation for use in specific clinical settings.

Estrogen Replacement Therapy—A Chronology

Premarin® (conjugated equine estrogens; CEE), first approved for use in 1942, contains a mixture of estrogens originally derived from the urine of pregnant mares.[7] This conjugated estrogen product has successfully controlled menopausal symptoms for countless millions of women around the world.

The present formulation of CEE has remained virtually unchanged for more than 60 years. A key feature of the Premarin® tablet is a protective coating consisting of pharmaceutical-grade shellac (extracted with alcohol from the shell of the Southeast Asian lacca beetle). This coating is designed to absorb oxygen and thus prevent the oxidation of constituent estrogens, while avoiding the escape of any distinctive odor or taste that might be associated with the active agents.

In the 1970s, the U.S. Food and Drug Administration (FDA) examined the 30 years of clinical experience with CEE, and determined that sufficient evidence was available to establish formal clinical indications for its use in controlling menopausal vasomotor symptoms and atrophic vaginitis. The FDA also concluded then that data were inadequate at that time to support its potential efficacy in protecting against the development of osteoporosis or reducing the long-term risk of cardiovascular events. Subsequently, more extensive clinical

studies were undertaken, which ultimately led to the 1986 approval of the indication for use of this ERT product in preventing osteoporosis.[4]

During the 1970s and 1980s, a number of estrogen formulations derived from sources other than pregnant mares' urine also received FDA approval for clinical use. Following more in-depth analysis of the Premarin® product formulation by FDA and the U.S. Pharmacopeia (USP), it was concluded that the principal active ingredients of CEE were sodium estrone sulfate and sodium equilin sulfate.[8] However, relatively little effort was made to compare the varying compositions of each of the marketed estrogen products with regard to such considerations as dissolution characteristics and pharmacologic equivalency.

This situation changed in 1984 with congressional approval of the Hatch-Waxman Act, which significantly expanded previously existing drug regulatory requirements. This legislation required the documentation of "generic equivalency"—that is, that varying formulations of any specific pharmacologic agent have the same chemical composition, as well as the same rate and extent of absorption, as the original branded product. To meet this new regulatory standard, formal dissolution testing on Premarin® was conducted by the FDA in 1986.[4]

Dissolution Characteristics of Slow-Absorption CEE

Following initial completion of dissolution testing of CEE, it was determined for the first time that CEE appeared to function as a modified-release agent—that is, the component estrogens did not dissolve immediately in water but rather were found to do so over time. This slowed dissolution profile appeared to be a characteristic of the shellac coating of the Premarin® tablet, particularly at acidic pH levels.[4,9] In comparison, other "generic estrogen" products then available demonstrated immediate-release dissolution profiles, suggesting the likelihood that there would be significant differences in estrogen blood levels depending upon the nature of each individual product's specific absorption characteristics.[4]

These findings led, in turn, to a series of FDA Advisory Committee meetings designed to assess the potential impact on safety and efficacy of the immediate dissolution of conjugated estrogens compared to the modified-release characteristics of CEE with the shellac coating

(Premarin®). The Advisory Committee findings eventually appeared in The Federal Register in 1990.[4] They concluded that while extensive clinical study data on this question were still lacking, it appeared likely that excessively high blood levels of estrogen resulting from use of an immediate-release product raised potentially significant safety issues. In addition to the immediate release of estrogen causing higher blood estrogen levels and thus such possible adverse effects as breast tenderness, the risk of breast cancer—which was deemed to be a dose-related effect—might also be increased compared to an estrogen formulation with a modified-release dissolution profile.[4,5,10]

The Advisory Committee also raised similar questions with regard to the efficacy of immediate-release estrogen products in terms of ensuring the long-term prevention of osteoporosis. They concluded that following the initial appearance of higher blood concentrations of estrogen, failure to maintain sufficient levels continuously throughout the day may inadequately stimulate the targeted estrogen receptors, thus providing sub-optimal bone protection. This issue was of particular long-term concern, since two or more years of careful monitoring are required in order to ensure that the estrogens are effective in reducing a woman's risk of osteoporosis.

Accordingly, the FDA concluded that it was necessary to remove all "generic", immediate-release estrogen products from the market.[4] This was then followed in 1992 by the development of FDA guidelines for the conduct of bioequivalency trials, to demonstrate that any new estrogen-replacement formulation possessed dissolution characteristics that mirrored those of slow-release CEE.[5] However, in attempting to establish uniform *in vitro* dissolution characteristics of Premarin® for purposes of such bioequivalency comparisons, it was discovered that in fact CEE dissolved at an inconsistent rate, varying widely not only from batch to batch but also between individual tablets.[11] This variability is likely due, at least in part, to the physical characteristics of the shellac coating applied to Premarin® tablets. Over time, the protective shellac oxidizes and tends to crack, permitting older tablets to dissolve more rapidly. Over the past 18 months alone, failure in dissolution testing has led to a number of large recalls, now approaching a total of 500 million Premarin® tablets.[12,13] Most of these product recalls appear to have involved tablets that had been manufactured a year or more prior to their recall.

Shellac exhibits only very limited solubility in an acidic solution,

making its dissolution profile highly dependent on an individual patient's gastric pH.[9] As a result, Premarin® tablets that have an intact shellac coating may pass through the highly acidic stomach undissolved, and enter the intestine where the pH begins to increase, ultimately reaching a level of about 6.8-7.0. As pH continues to rise, the shellac coating can soften and begin to disintegrate, permitting the CEE tablet to dissolve and the estrogenic components to be absorbed into the bloodstream.[9] When the shellac coating is compromised, this mechanism can fail and lead to dissolution and bioequivalency differences.

Cenestin® (Synthetic Conjugated Estrogens, A)

The only other oral ERT agent besides Premarin® that is currently classified as a modified-release product is Cenestin®, which consists of a mixture of 9 synthetic estrogenic substances in precisely controlled proportions. In addition to sodium estrone sulfate and sodium equilin sulfate, the major biologically active components, this product includes sodium 17α-dihydroequilin sulfate, sodium 17α-estradiol sulfate, sodium equilenin sulfate, sodium 17β-dihydroequilenin sulfate, sodium 17β-dihydroequilin sulfate, sodium 17β-estradiol sulfate, and sodium 17α-dihydroequilenin sulfate.

Unlike the shellac coating of Premarin® tablets, Cenestin® employs a multiple-layer polymer that works by hydration. This film-coating features a gum core matrix that releases the component conjugated estrogens in a highly consistent and predictable manner. The outer layer erodes upon exposure to fluid, which permits the estrogen within that layer to diffuse out of the tablet and exposes each progressively lower layer to the hydration process. *In vitro* testing has shown that the dissolution of Cenestin® is moisture-controlled, predictable, and independent of pH.[6,11]

As a result of its consistent dissolution characteristics, a recent study confirmed that blood estrogen concentrations with a once-daily dosing regimen of Cenestin® are relatively smooth and predictable.[6] This contrasts with the wide variability in blood levels that have been reported with Premarin® tablets (Table 1, Figure 1).[14] This could be even more clinically significant when the impact of gastric pH on CEE tablet dissolution characteristics is considered. The concomitant administration of drugs that neutralize the stomach pH, such as

TABLE 1. Percentage deviation in estrone and equilin release from an ideal Higuchi release pattern.

	Estrone		Equilin	
	α%		α%	
Time (hr)	Cenestin®	Premarin®	Cenestin®	Premarin®
.00	-32.3	-85.2	-39.8	-86.5
.00	-18.4	-56.9	-26.6	-57.9
.00	-1.9	-14.2	-11.8	-15.9
.00	+7.9	+13.5	-3.1	+12.8
.00	+14.2	+25.3	+3.0	+27.2
.50	+17.5	+28.3	+6.4	+32.2
.00	+17.4	+24.5	+7.0	+29.4
2.00	+9.0	+11.0	+0.3	+14.8

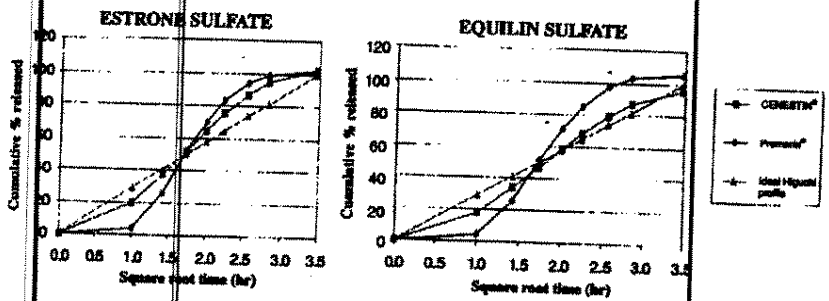

FIGURE 1. Percentage deviation in release profile of Cenestin® and Premarin® following Higuchi kinetics from an ideal Higuchi (12 hr) release profile.

antacids used to treat a co-existing GERD condition or calcium supplementation commonly taken by post-menopausal women (Table 2), could in turn lead to early CEE tablet dissolution.

In a recent *in vitro* study, investigators compared the well-established ideal dissolution profile (Higuchi release kinetics)—which has been developed for slow-release pharmaceutical formulations—to the concentrations of estrone sulfate and equilin sulfate actually observed at each of 9 distinct time points following the dissolution of Premarin® and Cenestin® tablets.[15] Throughout the 12-hour study, estrogen re-

TABLE 2. Medications that increase gastric pH.

Antacids
Calcium carbonate (Tums®)
Aluminum hydroxide (Alugel®)
Magnesium hydroxide (Maalox®)
Sodium bicarbonate (Soda Mint®)
H_2-antagonists
Cimetidine (Tagamet®)
Famotidine (Pepcid®)
Nizatidine (Axid®)
Ranitidine (Zantac®)
Proton Pump Inhibitors
Omeprazole (Prilosec®)
Lansoprazole (Prevacid®)
Pantoprazole (Protonix®)
Rabeprazole (Aciphex®)
Other
Misoprostol (Cytotec®)
Sucralfate (Carafate®)

lease with Cenestin® more closely followed the linear Higuchi profile, while Premarin® exhibited larger deviations from the ideal pattern at all time points. On average, between 2 and 5 hours after dissolution, Cenestin® released from 34% to 38% of its labeled conjugated estrogens (a typical slow-release profile), compared with nearly 60% for Premarin®.[7] The investigators concluded that estrogen release with Premarin® more closely resembled the pattern typically seen with a delayed "burst-like" drug release profile, rather than the slower but constant steady-state drug release profile with Cenestin®.

Early reports of clinical experience with Cenestin® are consistent with what would be expected from controlled slow dissolution, absorption and constant steady-state blood levels of estrogen. Patients report experiencing overall improvement in their quality of life with the use of this ERT product compared to other estrogen formulations. Specifically, as might be expected, patients have reported far less breast tenderness, headache, mood swings, bleeding and night sweats with Cenestin® than with other oral estrogen formulations (Hess, personal communication).

Implications of the Concomitant Administration of Acid-Reducing Therapy and ERT

The most frequent cause of dyspepsia, gastroesophageal reflux disease (GERD) is a widespread condition that has been estimated to affect as many as 50% of all adults in any given year.[16] GERD generally manifests as heartburn (pyrosis), the well-recognized sensation of substernal burning and discomfort that is often associated with regurgitation of acid-peptic gastric juice into the esophagus.

The goal of the clinical management of GERD is the elevation of gastric pH and reduction of acid regurgitation. Over-the-counter antacids, H_2-receptor antagonists (e.g., cimetidine, ranitidine) and proton pump inhibitors (e.g., omeprazole, lansoprazole) are now widely used in the treatment of this common condition (Table 2).[17] Proton pump inhibitors are among the most frequently prescribed of these medications, and cause prolonged and profound elevations of gastric pH. In addition, current treatment guidelines suggest that post-menopausal women should receive daily calcium supplementation, a recommendation that patients frequently observe by taking a widely-used antacid such as Tums®.[18]

However, the potential ramifications of neutralizing the acidic stomach pH in those women who are also receiving ERT are often not taken into consideration when prescribing estrogen replacement therapy. For example, the increase in stomach pH arising from the use of an acid-reducing medication by patients also taking CEE tablets may quickly erode even an intact shellac coating. This could lead to earlier tablet dissolution, resulting in a rapid rise in blood estrogen concentrations to levels that are more typical of an immediate-release estrogenic formulation. It is also likely that polymer-based formulations, such as Cenestin®, are less vulnerable to changes in gastric pH resulting in sustained and predictable plasma estrogen concentrations. Obviously, controlled pharmacokinetic trials designed to compare the effect of pH-altering medications on the absorption of estrogen from various ERT formulations are needed.

This development raises potential issues with respect to both the efficacy and safety of estrogen replacement therapy with CEE, possibly negating the clinical benefits of its slow-release estrogenic dissolution profile. As was recently observed by Speroff, "... an important clinical principle is the following: duration of exposure to a hormone is as important as dose."[19] As the most troublesome vasomotor symp-

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toms of menopause frequently occur at night (e.g., night sweats) and may disrupt sleep, an ERT preparation taken in the morning should ideally continue to release estrogen over the course of the day. However, if a modified-release product's dissolution profile more closely resembles that of an immediate-release formulation due to co-administration of an acid-lowering medication, it is less likely that estrogen concentrations sufficient to effectively control nighttime symptoms will be consistently achieved. Other symptoms such as breast tenderness, mood swings and dysfunctional bleeding can similarly be affected by the burst effect.

By contrast, the tablet dissolution profile of Cenestin® is uniform and governed by the physical properties of its hydrophilic matrix film-coating, and should therefore be minimally affected by changes in pH along the gastrointestinal tract.

Potential Advantages of Lower-Dose Estrogen Supplementation

It is well recognized that more than half of all women who receive ERT discontinue this treatment within 2-3 years, due to concern over long-term safety as well as the development of side effects such as breast tenderness, bleeding and concern over breast cancer.[20] This issue has been dramatically highlighted by the recent premature discontinuation of the combination hormone replacement therapy (Prempro™) arm of the comprehensive Women's Health Initiative study.[21]

To address these important clinical concerns, more recent research has been exploring the potential advantages of further reducing the dosage of estrogen treatment regimens to even smaller doses. With slow-release formulations producing constant steady-state estrogen levels, much smaller doses than would be needed with an immediate-release product may be effective. It is hoped that the results of these studies of very low-dose slow-release formulations will provide more effective yet safer therapy, and assist physicians in choosing the most appropriate ERT regimens for their patients.

Discussion and Conclusion

More than 60 years of clinical experience with estrogen replacement therapy has confirmed its important role in helping to control the

wide-ranging symptoms often experienced by many menopausal women. Regulatory Advisory Committees in the 1990s recognized the advantages of a modified- (or slow-) release estrogen formulation—namely, avoiding initially high estrogen concentrations that could lead to an elevated risk of side effects, as well as subsequently reduced blood levels that might provide inadequate estrogen receptor stimulation and thus decrease overall efficacy.

Over the past decade, significant advances in pharmaceutical product formulation technology have improved the process of drug delivery. These developments have led to dramatic improvements in tablet dissolution and absorption characteristics, compared with those technologies employed in older modified-release preparations.

Tablets of the original ERT product, conjugated equine estrogens (CEE, Premarin®), are coated with a pharmaceutical glaze (shellac) that has shown widely varying dissolution properties depending upon such factors as the age of the tablets and the pH to which the tablet is exposed *in vitro*. In particular, ingestion of over-the-counter antacids (such as Tums®) or a proton pump inhibitor to treat the symptoms of GERD, experienced by half of all adults, could lead to earlier tablet dissolution and more rapid absorption of the component estrogens from concomitantly-administered CEE.

The only other modified-release conjugated estrogens preparation currently marketed, plant-derived synthetic conjugated estrogens, A (Cenestin®), employs a unique slow-release technology. Estrogens are absorbed from this product formulation in a consistent and predictable pattern with once-daily dosing, maintaining uniform estrogen concentrations, and are independent of gastric pH. Comparative *in vitro* studies have shown that the Cenestin® preparation exhibits an estrogen-release profile that more closely follows the ideal, slow-release Higuchi dissolution profile compared to Premarin®. However, while these findings have been noted, their clinical implications have yet to be fully elucidated.

Since a majority of women who are prescribed ERT discontinue treatment within 2-3 years, recent research efforts have focused on the use of lower-dose estrogen regimens in order to help reduce any associated risks while retaining the important clinical benefits of this therapy. Current strategies involve selection of a modified-release preparation with a uniform absorption profile to improve the consistency and predictability of estrogen blood concentrations over 24 hours,

thereby reducing unwanted side effects and maximizing the potential for therapeutic success.

References

1. Taylor M: Alternatives to conventional hormone replacement therapy. *Complement Ther. Med. 23*:514-532, 1997.
2. Notelovitz M, Lenihan JP, McDermott M, et al.: Initial 17β-estradiol dose for treating vasomotor symptoms. *Obstet. Gynecol. 95*(5):726-731, 2000.
3. Speroff L, Rowan J, Symons J, et al.: The comparative effect on bone density, endometrium, and lipids of continuous hormones as replacement therapy (CHART study). *JAMA 276*(17):1397-1403, 1996.
4. U.S. Food and Drug Administration: Abbreviated New Drug Applications for conjugated estrogens; proposal to withdraw approval; opportunity for a hearing. *Federal Register 55*(30):5074-5078, 1990.
5. U.S. Food and Drug Administration: Guidance—Conjugated estrogens tablets in vivo bioequivalence and in vitro drug release. August 21, 1991.
6. Stevens RE, Roy P and Phelps KV: Evaluation of single- and multiple-dose pharmacokinetics of synthetic conjugated estrogens, A (Cenestin®) tablets: A slow-release estrogen replacement product. *J. Clin. Pharmacol. 42*:332-341, 2002.
7. Klein R: The composition of Premarin. *Int. J. Fertil. 43*:223, 1998.
8. Premarin® (conjugated estrogens) prescribing information. *In*: Physician's Desk Reference, 57th Ed. Thomson PDR, Montvale, NJ, 2003, p. 3444.
9. Specht F, Saugestad M, Waaler T and Muller BW: The application of shellac as an acidic polymer for enteric coating. *Pharmaceutical Technology Europe 9*:20-28, 1998.
10. Varma TR, Everard D and Hole D: Effect of natural estrogen on the serum level of follicle stimulating hormone (FSH), estradiol and estrone in post-menopausal women and its effect on endometrium. *Acta Obstet. Gynecol. Scand. 64*(2):105-109, 1985.
11. Data on file, Duramed Pharmaceuticals Inc.
12. FDA Recalls and Court Actions, March 27, 2002. *Prescription Pharmaceuticals and Biotechnology—"The Pink Sheet" 64*(14):34-36, April 8, 2002.
13. *Safety Alerts*, August 21, 2002.
14. A single and multiple dose pharmacokinetic study on the effects of dose and rate of absorption on plasma levels of Premarin® and its metabolites following tablet and oral solution administration: Interim analysis. FDA Docket No. 94P-0429, Vol. 6, May 5, 1997. Wyeth-Ayerst Laboratories, Philadelphia, PA.
15. Roy P, Stevens RE, Fredricks E and Phelps KV: Application of apparent first-order Higuchi release kinetics to compare two slow-release conjugated estrogens formulations: Synthetic conjugated estrogens, A (Cenestin®) versus conjugated estrogens, USP (Premarin®). Presented at the American Association of Pharmaceutical Scientists annual meeting, Denver, CO, October 21-25, 2001.
16. Locke GR, Talley NJ, Fett SL, et al.: Prevalence and clinical spectrum of gastro-esophageal reflux: A population-based study in Olmsted County, Minnesota. *Gastroenterology 112*(5):1448-1456, 1997.

17. DeVault KR and Castell DO: Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. *Am. J. Gastroenterol. 94*(6):1434-1442, 1999.
18. Gamble CL: Osteoporosis: Drug and non-drug therapies for the patient at risk. *Geriatrics 50*(9):39-43, 1995.
19. Speroff L: A clinical understanding of the estrogen receptor. *Ann. N.Y. Acad. Sci. 900*:26-39, 2000.
20. Berman RS: Patient compliance of women taking estrogen replacement therapy. *Drug Inf. J. 31*:71-83, 1997.
21. Writing Group for the Women's Health Initiative Investigators: Risks and benefits of estrogen plus progestin in healthy postmenopausal women. *JAMA 288*:321-333, 2002.